Cover Page

Official title: Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis ECZTRA 6 (ECZema TRAlokinumab trial no. 6)
LEO Pharma number: LP0162-1334
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Statistical Analysis Plan

Tralokinumab monotherapy for moderate-to-severe atopic dermatitis
ECZTRA 6 (ECZema TRAlokinumab trial no. 6)

Phase 3 – Efficacy and safety trial

A randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial to evaluate the efficacy, safety and tolerability of tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy

LEO Pharma A/S	**Trial ID:**	**LP0162-1334**
	Date:	**23-APR-2021**
	Version:	**v1.0**

1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Medical Lead, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD , MSc Stat

Biostatistics Lead, Medical Sciences

PPD , MD

Medical Lead, Medical Sciences

PPD , MSc PhD

QC Statistician, Biostatistics and Pharmacoepidemiology

2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan is designed to comply with the standards issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice, and E9: Statistical Principles for Clinical Trials).

Table of Contents

3 List of Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibodies
ADaM	Analysis data model
AE	Adverse event
ATC	Anatomical therapeutic chemical
CDLQI	Children's Dermatology Life Quality Index
COVID-19	Coronavirus disease 2019
EASI	Eczema Area and Severity Index
EASI50	At least 50% reduction in EASI score
EASI75	At least 75% reduction in EASI score
EASI90	At least 90% reduction in EASI score
ECG	Electrocardiogram
FAS	Full analysis set
FDA	US. Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator’s Global Assessment
IMP	Investigational medicinal product
LOCF	Last observation carried forward
MAR	Missing at random
NRS	Numeric Rating Scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
POEM	Patient Oriented Eczema Measure
Q2W	Every 2 weeks
Q4W	Every 4 weeks

SCORAD	Scoring Atopic Dermatitis
TCI	Topical calcineurin inhibitors(s)
TCS	Topical corticosteroid(s)

4 Introduction

The statistical analysis will be performed as outlined in the Clinical Trial Protocol including amendments.

This Statistical Analysis Plan is prepared before the unblinding of the trial and supplements the Clinical Trial Protocol, which otherwise describes the originally planned statistical analyses of all endpoints in an intended exhaustive manner. The Statistical Analysis Plan contains a more technical and detailed elaboration of some points related to the implementation of the statistical analyses already described in the Clinical Trial Protocol.

In addition, the Statistical Analysis Plan includes supplementary statistical analyses and aspects that are not present in the latest protocol amendment.

Supplementary analyses introduced according to LEO response to FDA Advice letter dated CCI ; Ref ID: CCI :

1. A tipping point analysis introduced as a sensitivity analysis number 3 for the primary estimand ('composite') for the primary endpoints (IGA 0/1 and EASI75) and the secondary endpoint (reduction of Adolescent Pruritus NRS weekly average of at least 4 (yes/no)).
2. Analyses of a new tertiary estimand ('composite') for the continuous secondary confirmatory endpoints (change in SCORAD and change in CDLQI). Analyses apply non-responder imputation for subjects who received rescue medication. A tipping point sensitivity analysis is included.

Other supplementary analyses introduced for consistency:

3. The same analysis and tipping point sensitivity analysis as above implemented as a new tertiary ('composite') estimand for the two secondary additional endpoints 'Change from baseline to Week 16 in EASI score' and 'Change from baseline to Week 16 in Adolescent Pruritus NRS (weekly average)'

The first aspect is addressed in section 6.7.1 , the 2nd and 3rd are addressed in section 6.7.2 and 6.7.4, respectively.

5 Trial Analysis Sets

The trial analysis sets are defined in the protocol and the following modifications to the analysis sets are introduced.

At sites PPD (n=2) and PPD (n=7) several critical GCP non-compliance issues have been identified. At site PPD the validity of key eligibility criteria (e.g. AD diagnosis and disease severity) for the 2 subjects has been questioned. Site PPD was closed due to findings in other ECZTRA trials where e.g. the AD diagnosis, exposure to IMP and safety collection were questioned. In LP0162-1334, similar findings have been detected. It can not be confirmed that subjects from site PPD and PPD do represent the targeted population of adolescents with moderate-to-severe AD. Therefore, subjects from the two sites will be excluded from the analyses sets and will be reported separately in listings and tables, as appropriate.

All subjects randomised to initial treatment who were exposed to IMP and not being from sites PPD and PPD are included in the full analysis set (FAS) and will be analysed for efficacy up to Week 16 (visit 11). For subjects not exposed to IMP, the decision to withdraw cannot be biased by knowledge of the assigned treatment due to the blinding. This definition of the FAS implements the consideration mentioned in the protocol regarding exclusion of randomized subjects per ICH E9, Section 5.2.1.

The safety analysis set comprises all subjects randomised to initial treatment who were exposed to IMP and not being from sites PPD and PPD The protocol further specifies to exclude subjects from the safety analysis set for whom no post-baseline safety data are available. However, since all subjects receive the first dose of IMP in connection with the Week 0 visit and are subsequently monitored for immediate drug reactions, all exposed subjects are considered to have post-baseline safety data available and no such further exclusions will be made.

The maintenance analysis set is defined in the protocol as all subjects who receive tralokinumab in the initial treatment period and who are re-randomised to maintenance treatment. In addition to this, subjects who are not exposed to maintenance treatment and subjects from sites PPD and PPD will be excluded from the maintenance analysis set. This follows the same principle that leads to exclusion of unexposed subjects from the full analysis set and is in alignment with ICH E9.

The maintenance safety analysis set comprises all subjects who are re-randomised, not being from sites PPD and PPD and receive at least one dose of maintenance treatment.

The open-label safety analysis set comprises all subjects (except those from sites PPD and PPD who at any point in time enter the open-label treatment arm and receive at least one dose of open-label treatment.

For the follow-up period, the safety follow-up analysis set will be used as the basis for evaluation of adverse events during the follow-up period. It comprises all subjects (except those from sites PPD and PPD for whom date of last contact is after the date of exposure end, where exposure end is defined as the Week 52 visit for subjects completing the treatment period, and otherwise the date of permanent discontinuation of IMP for subjects not completing the treatment period. See also section 6.12.2 for further details.

For analysis of efficacy, subjects will be included ‘as randomised’.

For analysis of safety, if a subject is mistakenly given an experimental therapy other than that to which they were randomized, they should be analyzed ‘as-treated’, thus included in the group according to the therapy actually received by the subject. The below rules will be applied:

1) Subjects who received at least one dose of tralokinumab during the initial treatment period will be assigned to one of the tralokinumab treatment groups according to the rules below. Although this may dilute the AE rate in the tralokinumab treatment group slightly by including in the denominator e.g. subjects who only received one dose of active

treatment, it will ensure that no significant drug reactions to tralokinumab will erroneously be assigned to placebo. Subjects will be analysed according to the highest dose received, i.e.

a) Tralokinumab 300mg if at least one dose of Tralokinumab 300mg
b) Tralokinumab 150mg if at least one dose of Tralokinumab 150mg and no doses of Tralokinumab 300mg
c) Placebo if no active doses

2) Subjects in the maintenance safety analysis set will be analysed as follows: Week 16 Tralokinumab responders will be displayed in tables for the maintenance period according to actual treatment defined as:
   a) Tralokinumab 300mg Q2W if the maximum dose was Tralokinumab 300mg, and at least two subsequent active doses were administered
   b) Tralokinumab 150mg Q2W if the maximum dose was Tralokinumab 150 mg, and at least two subsequent active doses were administered
   c) Tralokinumab 300mg Q4W if the maximum dose was Tralokinumab 300mg, but no two subsequent active doses were given without an intermediate placebo dosing
   d) Tralokinumab 150mg Q4W if the maximum dose was Tralokinumab 150mg, but no two subsequent active doses were given without an intermediate placebo dosing

In case subject withdrew after the first dose, the subject will be assigned to 150 or 300 mg according to which dose was given, and Q2W/Q4W according to the randomization. Week 16 placebo responders will be displayed in the “Week 16 placebo responders / Placebo” column in summary tables, regardless of actual treatment received. Any deviations from the planned treatment regimen (i.e. if any active doses are given) will be described as protocol deviations.

6 Statistical Analysis

6.1 Aspects related to the COVID-19 pandemic

An urgent safety measure was implemented during the trial which allowed for collection of adverse events by phone if trial visits at site were not possible due to local preventive measures during the COVID-19 pandemic. As the influence of the COVID-19 pandemic on trial execution, data collection and safety of subjects are not amended in the protocol, this section is introduced to elaborate on the COVID-19 pandemic related aspects.

Collection of data at planned visits allows to report if data is missing due to the COVID-19 pandemic either due to the visit being performed via telephone, thereby only allowing for a subset of data being collected, or the visit being not done (no data collected).

Data collection in the initial treatment period is not affected by the COVID-19 pandemic due to the timing (all subjects passed Week 16 when the pandemic started), while the impact in the maintenance and open-label treatment periods as well as safety follow-up period is considered limited. The number and percentage of subjects having Week 48, Week 50, Week 52 and safety follow up visit being partially/not done due to COVID-19 will be reported as well as the number and percentage of individuals missing ADA samples at Week 28, Week 52 and safety follow-up visit. Week 48/50 is selected as this is the last dosing visit for Q4W/Q2W and Week 52 is selected as this is the final evaluation of efficacy and safety during the maintenance and open-label treatment periods. percentage of visits being partially done or not done and will be reported by treatment period.

In the context of efficacy analyses, a sensitivity analysis of response at Week 52 will be done where LOCF imputation will be used for subjects missing assessments at Week 52 due to COVID-19 pandemic instead of imputing data as non-responders.

6.2 Baseline characteristics

Demographics and baseline disease severity will be summarized for all randomised subjects and FAS.

Other baseline characteristics will be summarised for subjects in FAS only.

All baseline characteristics will be listed for all randomised subjects.

Baseline characteristics for subjects in FAS transferred to open-label treatment at Week 16 will be presented by previous treatment and overall.

Duration of AD in years will be calculated as (age at Week 0) minus (age at onset of AD).

The table of concomitant medication at baseline will include medication starting before the first dose of IMP and ongoing at the time of first dose of IMP. For further details, see Section 6.12.3 and Section 6.12.4.

In case a subject has been randomised based on a wrong value of a stratification variable, the correct value of the variable will always be used in descriptive statistics and analyses. Subject(s) who were randomised within a wrong stratum will be listed.

6.3 Disposition

Subject disposition will be summarised and listed.

6.4 Rescue medication

For initial and maintenance treatment period, rescue medication is defined by the following algorithm: Concomitant medications with Dermatitis atopic or Dermatitis infected as the preferred term for the indication and either ATC2 code H02 or D07, or ATC4 code D11AH or Preferred name Delgocitinib, Crisaborole, Methotrexate, Ciclosporin, Azathioprine, Mycophenolate-mofetil, Mycophenolate-sodium, Mycophenolate-acid, or Dupilumab.

For open label treatment period (where mild to moderate TCS and TCI were allowed), rescue medication is defined by the following algorithm: Concomitant medications with Dermatitis

atopic or Dermatitis infected as the preferred term for the indication and either ATC2 code H02, or ATC4 code D07AD, D07BD, D07CD or D07XD, or Preferred name Crisaborole, Delgocitinib, Methotrexate, Ciclosporin, Azathioprine, Mycophenolate-mofetil, Mycophenolate-sodium, Mycophenolate-acid, or Dupilumab.

According to the protocol investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. Therefore, if rescue medication has start date the same day as an efficacy assessment, then the assumption will be that the assessment is not influenced by the rescue medication, see also Section 6.12.4.

Rescue medication will be summarised separately for the initial, maintenance and open-label treatment period. In addition, a summary table of rescue medication by type (topical and systemic) and by overall group (corticosteroids, immunosuppressants and other) will be made. In addition, rescue medication during the initial treatment period taken between the Week 2 and Week 16 will also be summarised. Rescue medication during initial treatment period will include rescue medication taken between first dose and Week 16 visit. For subjects continuing with maintenance or open-label treatment at Week 16, the table of rescue medication during initial treatment period will include rescue medication taken between the first dose of initial treatment and the first dose of either maintenance or open-label treatment.

For subjects who do not continue with maintenance or open-label treatment, the table of rescue medication during initial treatment period will include medications taken after the first dose and before the Week 16 visit (if exists), otherwise before Day 112.

The table of rescue medication during the maintenance and open label treatment period will include rescue medication not ended during initial period as well as rescue medication initiated after the first maintenance and open label dose and exclude rescue medication initiated during the follow-up period.

6.5 Compliance

Compliance will be summarised and listed. The impact of COVID-19 pandemic on compliance will be also summarised.

6.6 Exposure

The exposure time during the initial, maintenance and open-label periods, respectively, will be defined as detailed in Section 6.12.1. Exposure time will be summarised and listed.

Patient years of exposure (PYE) for a period will be calculated as the difference between the start date and time and the end date and time for the period divided by 60x60x24x365.25.

6.7 Analysis of efficacy

6.7.1 Primary and secondary binary endpoints

Sensitivity analysis 2 for the primary estimand (primary endpoints)

In the sensitivity analysis 2 for the primary estimand, the protocol specifies that "If subjects have withdrawn due to an AE or due to lack of efficacy, they are still considered non-responders". For clarification, such subjects will be identified based on their reason for permanent discontinuation of IMP.

Sensitivity analysis 3 for the primary estimand (binary endpoints)

A tipping point analysis using multiple imputation (MI) as an additional sensitivity analysis (not described in the protocol) for the primary estimand for the primary endpoints (IGA 0/1 and EASI75) and the secondary binary endpoint (reduction of Adolescent Pruritus NRS weekly average of at least 4 (yes/no); Adolescent Pruritus NRS ≥ 4) will be done.

The purpose of the sensitivity analysis is to assess the robustness of results of the primary analysis for the primary estimand with respect to the assumption regarding missing Week 16 data among subjects who did not use any rescue medication from Week 2 to Week 16. The procedure will be as follows: subjects in the tralokinumab arms with missing Week 16 data will per default be considered non-responders while missing Week 16 data (i.e. response yes

(=1)/ no (=0)) for subjects in the placebo arm who did not use rescue medication from Week 2 to Week 16 will be imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p, different percentages of placebo subjects will be assumed to be responders (deviating from the default zero (0) percent of the primary estimand).

Based on published data from another placebo-controlled clinical trial conducted in adolescents with moderate-severe atopic dermatitis (2), the response rate for IGA 0/1, EASI75 and Adolescent Pruritus NRS ≥ 4 at Week 16 among all placebo subjects is low (in the order of 2.4% for IGA 0/1, 8.2% for EASI75 and 4.8% for Adolescent Pruritus NRS ≥ 4). Thus, a tipping-point value (p) above 0.05 for IGA 0/1 and Adolescent Pruritus NRS ≥ 4 and above 0.10 for EASI75, respectively, is not considered to be clinically plausible. As indicated above, p=0 corresponds to the primary analysis for the primary estimand. The MI procedure will include the following steps for each value of p:

- 100 copies of the dataset will be generated (seed=11109934). and missing Week 16 data will be imputed for subjects in the placebo arm from a Bernoulli distribution with parameter p.

- For each of the 100 complete data sets, the difference in response rates will be analysed as specified for the primary analysis for the primary estimand and the estimates and standard errors from the 100 analyses will be combined using Rubin's rule to form a unique point estimate and standard error.

- For each of the active treatment groups, the tipping point is calculated as the smallest placebo response rate where the p-value exceeds the nominal significance level alpha. If all p-values are below alpha, tipping point is coded as "Not reached". If the original analysis (i.e. response rate =0) already does not reach nominal significance, the tipping point is coded as "Not applicable".

6.7.2 Continuous secondary endpoints

Primary analysis of primary estimand (continuous secondary endpoints)

It is specified in the protocol that the continuous secondary endpoints will be analysed using a repeated measurements model on the post baseline responses up to Week 16. Data collected after permanent discontinuation of IMP or after initiation of rescue medication between Week 2 and 16 will not be included in the analysis.

However, some subjects may not have any post-baseline data collected before initiation of rescue medication. To ensure that all subjects are included in the analysis, the baseline value for these subjects and other subjects with no post baseline data will be carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment.

Tertiary (composite) estimand (continuous secondary endpoints)

For the continuous secondary endpoints (i.e. change in SCORAD and CDLQI), an analysis is introduced where subjects who received rescue medication between Week 2 and 16 are considered non-responders. This new analysis aims to estimate the treatment effect for a ‘Composite‘ estimand which is currently not pre-specified in the protocol for the continuous secondary endpoints. Thus, a new tertiary ‘Composite’ estimand for the continuous secondary endpoints is introduced.

Primary analysis for the tertiary (composite) estimand (continuous secondary endpoints): Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Subjects who have received rescue medication between Week 2 and Week 16 will be considered non-responders by using worst observation carried forward (including the baseline value).

Missing Week 16 data among subjects who did not use rescue medication will be imputed using MI (100 copies of the dataset, seed=11109934) assuming missing at random (MAR) within arms (based on sequential use of an ANCOVA model for Week 2, 4, 6, ... and 16). For subjects who dropout without any use of rescue medication, missing data at subsequent visits

will be imputed under the assumption that the subject adheres to the randomised treatment regimen, i.e. the stepwise imputation model will be estimated based on available data from all subjects but excluding individual subject data captured after initiation of rescue medication or permanent discontinuation of IMP. For each of the 100 imputed datasets, the continuous secondary endpoint will be analysed using an ANCOVA model with effects of treatment, region, baseline disease severity (IGA 3 or 4), and baseline value. The estimates and standard errors from the 100 analyses will be combined using Rubin's rule to form a unique point estimate and standard error.

As a sensitivity analysis for the tertiary estimand, a tipping point analysis using MI will be performed with the purpose to assess the robustness of results of the primary analysis for the tertiary estimand with respect to the MAR assumption regarding missing Week 16 data among subjects who did not use any rescue medication between Week 2 and 16. The tipping point analysis will assess how severe the departure from the MAR assumption in the tralokinumab arms has to be in order to impact the results (i.e. changes the conclusion of primary analysis of the tertiary estimand) from significant to non-significant).

- The tipping point analysis will be performed using the MAR imputed Week 16 data from primary analysis of the tertiary estimand. For each of the 100 imputed datasets, Δ will be added to the imputed values for subjects in the tralokinumab arms i.e. same Δ in the two tralokinumab treatment arms, ($\Delta = 0$ implies MAR) and thereby the imputed values will be 'shifted' by Δ. Each of the 100 modified imputed datasets will then be analysed in the same way as for the primary analysis for the tertiary estimand and tested using the same procedure. For each of the active treatment groups, the tipping point is calculated as the smallest delta where the p-value exceeds the nominal significance level alpha.

Tertiary (composite) estimand (continuous additional secondary endpoints)

The two continuous secondary additional endpoints 'Change from baseline to Week 16 in EASI score' and 'Change from baseline to Week 16 in Adolescent Pruritus NRS (weekly average)' will be analysed as described for the two continuous secondary endpoints above, including the tipping point sensitivity analysis.

6.7.3 Multiple imputation

For the analysis of the primary and secondary endpoints, multiple imputation will be carried out as specified in the protocol, using SAS PROC MI. For multiple imputations related to the treatment policy estimand and the hypothetical estimand sensitivity analyses, the seed 11109934 will be used. The remaining seeds are specified in the protocol.

When performing multiple imputation of continuous parameter values, imputed values at visits prior to Week 16 outside the relevant parameter scale shall be used as is. Values imputed at Week 16 shall be truncated to the nearest upper or lower bound on the given scale. For example, negative imputed EASI values at Week 16 will be set to 0.

For imputation of IGA values, the LIKELIHOOD=AUGMENT option will be used (1).

For imputation of IGA values, it may occur that the observed data from which the imputation model is fitted does not contain all levels of the IGA predictors necessary for the imputation. For example, the imputation model for IGA values at Week 8 will be based on observed data from the subset of subjects with observed IGA values at both Week 6 and Week 8. If only the IGA values (0,1,2,3) are observed at Week 6 in this subset of subjects, the imputation model will not be able to predict IGA values at Week 8 for a subject with an IGA value of 4 at Week 6. To avoid this situation, in this specific example IGA values of 3 and 4 at Week 6 will be combined into a single category for the imputation. In general, if this situation arises, IGA categories will be combined into a single category at the specific visit for the specific imputation, according to the rules in Table 1.

Table 1: Adjacent IGA categories combined in case of missing predictors in observed data

IGA value(s) missing in imputation model	**IGA categories combined**
0	(0,1)
1	(0,1)
2	(2,3)
3	(2,3)
4	(3,4)

Only three individuals discontinuing the treatment in the initial treatment period are having data observed at Week 16, hence there is no possibility of multiple imputations within the groups as defined in the protocol for a primary analysis for the treatment policy estimand for both binary and continuous endpoints. Omitting all factors in the imputation model (region and baseline effects) as well as treatment group and few subjects with missing data among those that do not discontinue the treatment, results in no or trivial variation between the imputed data sets; hence the primary analysis for the treatment policy estimand is omitted.

For the continuous endpoints, in the sensitivity analysis for the treatment policy estimand, data from the three subjects is used to impute data for all subjects with missing data at Week 16 and who discontinued treatment prior to Week 16 disregarding treatment, region and baseline characteristics in the imputation model. For subjects who have not discontinued treatment prior Week 16, missing data is imputed from subjects from the placebo arm who have not discontinued treatment prior to Week 16.

6.7.4 Secondary and other efficacy analysis

Reduction of Adolescent Pruritus NRS weekly average of at least 4

The analyses will be based on subjects in the FAS with a baseline Adolescent Pruritus NRS weekly average of at least 4.

Calculation of Weekly average of Adolescent Pruritus NRS

The weekly average will only be calculated if at least 4 assessment are available. When calculating the baseline value for the weekly average of Adolescent Pruritus, the daily assessments in the 7 days preceding the randomisation will be used, including the day of randomisation.

For the initial treatment period, the NRS weekly average for Week 1 will be calculated based on scores recorded on day 1 to day 7 (where day 0 is the day of the first dose). Similarly, for Weeks 2 to Week 15, the weekly average for Week x will be calculated based on scores recorded on day 7*x-6 to day 7*x (where day 0 is the day of first dose). Since maintenance and open label treatment may be initiated between day 106 and day 112, the Week 16 weekly average will instead be based on the last 7 days before (and including) the day of the Week 16 visit, thus ensuring that the Week 16 weekly average is based on data from the initial treatment phase only and ensuring alignment in timing with other Week 16 efficacy endpoints. Also, for the calculation of Week 1 to Week 15 weekly averages, any scores recorded after the Week 16 visit date will be disregarded (only relevant if Week 16 visit is out of window).

For Week 17 of the maintenance and open label treatment period, the weekly average will be based on the first 7 days after (not including) the Week 16 visit. For Week 18 to Week 52 of the maintenance or open-label treatment period, the weekly average for Week x will be calculated based on scores recorded on day 7*x-6 to day 7*x (where day 0 is the day of the first dose).

Additional analyses of patient-reported outcomes

Adolescent PGI-S (today's recall) is not numerical, the worst score recorded during the week will be presented instead of weekly average. The worst score will be derived if at least one measurement is available for the week in question. The same rules regarding visit windowing apply as for weekly average pruritus NRS described above. The worst scores will be presented graphically.

Clinically meaningful improvement from baseline in CDLQI and POEM of at least 4 and 6 points improvement will be assessed in the initial treatment period by visit using the primary analysis for the composite estimand approach for binary endpoints. Subjects contributing to the analysis will be those subjects with at least 4 and 6 points, respectively, at baseline.

Percentage change in EASI score, initial treatment period

In addition to the repeated measurements analysis of absolute reduction in EASI score during the initial treatment period, which was planned in the protocol, the same analysis will be conducted for the percentage change from baseline in EASI scores during the initial treatment period.

Subgroup analyses

To access consistency of number of responders for the primary and treatment policy estimand across subgroup the following subgroup analyses will be performed:

- IGA 0/1 by baseline IGA
- IGA 0/1 by region
- EASI75 by baseline IGA
- EASI75 by region

Maintenance analyses

As specified in the protocol, the maintenance of effect of tralokinumab will be evaluated at Week 52 for subjects who achieved clinical response at Week 16 without rescue medication . Subjects who have received rescue treatment between Week 16 and Week 52 will be considered non-responders. Missing data for subjects who did not attend the Week 52 visit and who did not use rescue treatment between Week 16 and Week 52 , will be imputed as non-responders. Additional analysis disregarding use of rescue will be performed (treatment policy approach).

In addition, response rate with the same handling of rescue medication and missing data as for Week 52 analysis and at each visit in the maintenance treatment period will be tabulated by treatment group.

Open label analyses

To evaluate the response rate in subjects who did not achieve IGA 0 or 1 or EASI 75 at week 16, IGA 0 /1, EASI75, EASI50, EASI90, SCORAD75, and CDLQI reduction from baseline of at least 4 and 6, POEM reduction from baseline of at least 4 and 6 and Adolescent Pruritus NRS reduction from baseline of at least 3 and 4, respectively, will be summarised in the OL period.

Summary will be done by visit, by initial treatment and as a total, for previously tralokinumab treated as a group and for both composite and treatment policy approach.

Scoring of PROs

CDLQI	Scored according to: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/childrens-dermatology-life-quality-index
POEM	Scored according to: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion.pdf
Adolescent PGI-S (past week recall, today recall)	https://www.fda.gov/media/116281/download
PGI-C	https://www.fda.gov/media/116281/download
HADS	The HADS consists of 14 items, 7 of which are related to anxiety and 7 related to depression. The maximum score is 21 for each subscale (anxiety and depression). If one question is missing within a subscale, the response to that question will be imputed as the mean of the remaining questions in that subscale. If more than one question is missing within a subscale, the subscale is considered missing (3).

Missing baseline assessments

When the baseline value is missing, endpoints concerning a change from baseline cannot be derived, and such subjects will be excluded from the analysis. Since the missingness of baseline values are unrelated to the assigned treatment, bias should not be a concern with this approach.

6.8 Analysis of safety

6.8.1 Adverse Events

Adverse events will be summarised and listed.

Assignment of AEs to periods

An adverse event will be assigned to a given period (initial, maintenance, open-label or follow-up) if the start date of the AE is after the start date and before the end date of that period (see Section 6.12.2, Table 3).

For AEs with start day on the same day as the first dose was given, only AEs starting after the first dose was given will be considered treatment emergent and assigned to the initial treatment period.

AEs with start date on the same day as the first dose of maintenance treatment will be assigned to the initial or maintenance period depending on whether the AE started before or after the dose was given.

AEs with start date on the same day as the first dose of open-label treatment will be assigned to the previous treatment period (can be initial or maintenance) or assigned to the open-label period depending on whether the AE started before or after the dose was given.

AEs starting on the day of exposure end (as defined in Section 6.12.2) will be assigned to the last treatment period.

For handling of incomplete start dates of adverse events, see Section 6.12.3.

Sort order of AE tables

Generally, AE tables by system organ class and/or preferred term will be sorted by decreasing number of affected subjects:

- For the initial treatment period, AE tables will be sorted by decreasing number of affected subjects in the Tralokinumab treatment groups (sum of 150 mg and 300 mg).
- For the maintenance treatment period, AE tables will be sorted by decreasing total number of affected subjects in the Tralokinumab treatment groups (sum of Q2W and Q4W groups in the maintenance treatment period).
- For the entire treatment period, AE tables will be sorted by decreasing number of affected subjects in the "Tralokinumab total" group (subjects being treated with Tralokinumab in at least one treatment period).
- For the follow-up period, AE tables will be sorted by decreasing total number of affected subjects in the Tralokinumab treatment groups (sum of tralokinumab 150mg/300mg Q2W/Q4W and Q2W+optional TCS groups in the safety follow-up period).

6.8.2 Vital signs

Vital signs will be summarised and listed.

For the summary tables of vital signs by visit, the last pre-dose vital sign assessment will be presented. If no dosing occurs at a visit, the last assessment recorded at the visit will be presented. For the first 3 IMP dosing visits in both the initial and open-label treatment period, subjects were monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, these measurements will only be listed.

6.8.3 ECG

ECG data will be summarised and listed. The overall central evaluation of ECG will be presented using shift tables.

6.8.4 Laboratory data

Laboratory data will be summarised and listed.

For the laboratory values, if the value is below the lower limit of quantification, half of the lower limit will be used for quantitative summaries. If the value is above the upper limit of quantification, the upper limit value will be used.

If more than one laboratory value is reported for the same visit and time point, the latest value will be used in summary statistics and analyses.

Laboratory parameters were classified as 'low', 'normal', or 'high', depending on whether the value was below, within or above the reference range, respectively. A shift table shows the categories at baseline against those at the end of a given treatment period. Subjects with laboratory parameters outside the reference range are listed. Reference ranges were based on subjects being fasting when the blood sample was taken. In the protocol, however, it was not a requirement that subjects were fasting when blood samples were taken. Therefore, some assessments may have been deemed above or below reference range for laboratory assessments where non-fasting samples would have resulted in a different reference range (e.g. glucose assessments). Additionally, the laboratory assigned the subject's age by year of birth, i.e. a subject born in December 2005 was assigned the age of 15 on 01-Jan-2020, almost a year before becoming 15 years old. This may have resulted in some assessments having been deemed outside reference range, as reference ranges differ significantly between different age groups.

Potentially clinically significant values will be defined as displayed in Table 2.

Table 2: Potentially clinically significant biochemistry and haematology values

Protocol Lab parameter	**SI Unit**	**PCS low**	**PCS High**
Biochemistry			
Sodium	mmol/L	< 129 mmol/L, < 125 mmol/L	> 160 mmol/L
Potassium	mmol/L	< 3 mmol/L, < 2.5 mmol/L	> 6.5 mmol/L, > 7.5 mmol/L
Creatinine	umol/L	N/A	> 1.5xULN, > 3xULN
Calcium	mmol/L	< 1.9 mmol/L	> 3.0 mmol/L, > 3.5 mmol/L
Alkaline phosphatase	U/L	N/A	> 1.5xULN

Aspartate aminotransferase	U/L	N/A	> 3xULN, > 5xULN, > 10xULN, > 20xULN
Alanine aminotransferase	U/L	N/A	> 3xULN, > 5xULN, > 10xULN, > 20xULN
Bilirubin	umol/L	N/A	> 2xULN
Cholesterol	mmol/L	N/A	> 6.2 mmol/L
LDL cholesterol	mmol/L	N/A	> 4.1 mmol/L, > 4.9 mmol/L
Triglycerides	mmol/L	N/A	> 2.3 mmol/L, > 5.6 mmol/L
Haematology			
Haemoglobin	g/L	< 90 g/L	> 190 g/L
Leucocytes	10^9/L	<4.0 10^9/L	>13.5 10^9/L
Neutrophils, absolute count	10^9/L	< 1.5 10^9/L, < 1.0 10^9/L, < 0.5 10^9/L	N/A
Lymphocytes, absolute count	10^9/L	< 0.6 x 10^9/L,	> 6.0 x 10^9/L
Monocytes, absolute count	10^9/L	< 0.4 x 10^9/L	> 0.9 x 10^9/L for female >1.3 x 10^9/L for male
Eosinophils, absolute count	10^9/L	N/A	>0.5 x 10^9/L > 1.5 x 10^9/L > 5.0 x 10^9/L
Basophils, absolute count	10^9/L	N/A	> 0.2 x 10^9/L
Thrombocytes	10^9/L	< 100 x 10^9/L,	> 700 x 10^9/L

PCS: potentially clinically significant; ULN: Upper limit of normal, i.e. upper limit of normal reference range. See leo/clinical/lp0162/1334/docs/adam/metadata/pcs/lb/LP0162-Adult_Adolescent_SAP_PCS values xlsx for details.

6.8.5 Urinalysis

Urinalysis data will be summarised and listed.

6.8.6 Pharmacokinetics and anti-drug antibodies

Pharmacokinetics and anti-drug antibodies data will be summarised and listed.

The ADA status will be categorised as follows:

- Positive
    1. Pre-existing: ADA-positive at baseline, no post-baseline ADA response ≥ 4-fold over baseline titre level, and at least 1 positive post-baseline ADA assessment.
    2. Treatment-boosted: ADA-positive at baseline and at least 1 post-baseline ADA response ≥ 4-fold over baseline titre level.
    3. Treatment-emergent: ADA negative or missing at baseline and at least 1 positive post-baseline ADA response.
- Perishing
    1. ADA positive at baseline, all post-baseline ADA assessments negative.
- Negative
    1. ADA negative or missing at baseline, all post-baseline ADA assessments negative.
- No post-baseline ADA assessment.

6.9 Biomarkers

Selected panel of serum biomarkers (periostin, TARC, S100A12, CCL11, CCL13, SIRT2, MMP12, IL-13, IL-16, IL-22, and IgE) will be summarized and change from baseline will be analysed as described in the protocol.

Blood transcriptomics's biomarkers (IFNG, IL-1A, IL-1B, IL-1RA, IL-1RACP, IL-1RL1ST, IL-2, IL-3RA, IL-4, IL-4R, IL-5RA, IL-6, IL-6R, IL-10, IL-13, IL-13RA1, IL-15, IL-18, IL-21, IL-23P19, CCL2, CCL22, CXCL1, CXCL9, CXCL10, RANBP3, S100A8, S100A9, S100A12, TNFa, OX40 and OX40L) will be summarized and analysed.

Reference genes selection and biomarker genes normalization

For each sample, the qualified reference genes from GUSB, RPLP0, RANBP3 and 18S will be used to normalise target gene measurement.

The raw Cycle threshold (Ct) values of reference genes are used for calculating gene-stability measure M using all samples (4). The reference genes with M<0.5 are selected and used for normalization of biomarker genes. The normalization is conducted per biomarker gene per sample, by subtracting Ct value of a biomarker gene from the geometric mean of selected reference genes from the same sample, resulting in a delta Ct (ΔCt) for each biomarker gene and sample. ΔCt represents a biomarker's mRNA assessment with a relative quantity in logarithm scale. The higher delta Ct is, the higher of mRNA quantity of a biomarker is.

Change from baseline to Week 16 (log_2 fold change) for each biomarker will be calculated as difference between the ΔCt at Week 16 and baseline. Log_2 fold change will be summarized per treatment arm and will be compared between each of the tralokinumab treatment groups and placebo using a Mann-Whitney test.

All biomarkers will be listed.

Summary and analysis of all biomarkers will be presented in a separate report.

6.10 Skin microbiology

Staphylococcus aureus colonization based on skin swab samples will be summarised and listed as described in the protocol.

High density data from skin microbiome sequencing will be presented in a separate report.

6.11 Skin barrier function

Selected panel of lipids from skin tape strips: cis-UCA, trans-UCA, PCA, 14:0-C18S, 16:0-C18S, 18:1-C18S, 28:0-C18S, 30:0-C18S, 32:0-C18S, 14:0-LPC, 16:0-LPC, 18:0-LPC, 26:0-LPC, 28:0-LPC, 30:0-LPC, EO26S18, EO34S18, EO26S22, EO34S22 will be summarized and analysed as described in the protocol.

All lipids will be listed.

90 samples will be analysed too late to be reported in the Clinical trial Report. Instead they will be reported in an addendum.

Summary and analysis of all lipids together with gene expression (RNA-seq) data will be presented in a separate report.

6.12 General Principles

6.12.1 Baseline value

Unless otherwise specified, the baseline value is defined as the latest pre-dose assessment.

6.12.2 Definition of trial periods and date of permanent discontinuation of IMP

Date of permanent discontinuation of IMP

Defined for subjects who have a reason for permanent discontinuation of IMP recorded.

The latest date of early termination visit (if existing) or date of onset of latest AE leading to withdrawal of trial product, otherwise date of the last visit, excluding safety follow-up and nominal Week 16 visit.

Exposure start

Date and time of first dose.

Exposure end

Date of Week 52 visit (if existing) at time 23:59:00, otherwise date of permanent discontinuation of IMP at time 23:59:00, or date of onset of latest AE leading to withdrawal of trial product, otherwise date of last IMP administration at time 23:59:00.

Trial periods

The time from exposure start to exposure end will be divided into initial period, maintenance period and open-label period, and remaining time after exposure end will be assigned to the follow-up period as shown in Table 3 (ADaM variable APHASE). The ADaM variable

APERIODC will indicate the latest treatment (initial, maintenance or open-label) at any given time point, thus not including a follow-up period Table 4.

Table 3: Start and end time of trial periods (ADaM variable APHASE).

APHASE	Start of period	End of period (only if start date exists)
Initial period	Exposure start	Date and time (minus 1 second) of first maintenance dose (if existing) else Date and time (minus 1 second) of first open-label dose (if existing) else Exposure end
Maintenance period	Date and time of first maintenance dose (if existing)	Date and time (minus 1 second) of first open-label dose (if existing) else Exposure end
Open-label period	Date and time of first open-label dose (if existing)	Exposure end
Follow-up period[1]	Exposure end (plus 1 second)	Date of last contact at time 23:59:00

1) Only applicable if date of last contact is not equal to date of exposure. Date of last contact does not include eDiary data records.

Table 4: Start and end time of trial periods (ADaM variable APERIOD).

APERIODC	Start of period	End of period (only if start date exists)
Initial period	Exposure start	Date and time (minus 1 second) of first maintenance dose (if existing) else Date and time (minus 1 second) of first open-label dose (if existing) else Date of last contact at time 23:59:00
Maintenance period	Date and time of first maintenance dose (if existing)	Date and time (minus 1 second) of first open-label dose (if existing) else Date of last contact at time 23:59:00
Open-label period	Date and time of first open-label dose (if existing)	Date of last contact at time 23:59:00

Date of last contact does not include eDiary data records.

6.12.3 Incomplete recordings

Adverse events

If the AE start day is missing, but AE start month and year are not missing, the following rules apply:

- If the year and month of the AE start is before the year and month of the exposure start, or if the AE end date is complete and before the exposure start, the AE will not be considered treatment emergent.
- If the year and month of the AE start is the same as the year and month of the exposure start, the AE will be considered treatment emergent and assigned to the initial treatment period, unless the AE has a complete end date which is before exposure start.
- If the year and month of the AE start is after the year and month of exposure start, it will be assumed that the AE started on the first day of the month and the AE will be assigned to the initial, maintenance, open-label , or follow-up period accordingly.

If the AE start month is missing, but AE start year is not missing, the following rules apply:

- If the year of the AE start is before the year of the exposure start, or if the AE end month is not missing and before the month of the exposure start, or if the AE has a complete end date which is before the exposure start date, the AE will not be considered treatment emergent.
- If the year of the AE start is the same as the year of the exposure start, the AE will be considered treatment emergent and assigned to the initial treatment period, unless the AE end month is not missing and before the month of the exposure start or the AE has a complete end date which is before the exposure start date.

- If the year of the AE start is after the year of exposure start, it will be assumed that the AE started on the 01 January and the AE will be assigned to the initial, maintenance, open-label, or follow-up period accordingly.

Concomitant medication

For incomplete start dates of concomitant medication, the following rules apply:

- If a medication start day is missing, but start month and year is not missing, it will be assumed that the start day is the first day of the month. If the medication start day and month is missing, but start year is not missing, it will be assumed that the start day is 01 January. If the medication start day, month and year is missing, it will be assumed that the medication was started before study start.

For incomplete end dates of concomitant medication, the following rules apply:

- If a medication end day is missing, but end month and year is not missing, it will be assumed that the end day is the last day of the month. If the medication end day and month is missing, but end year is not missing, it will be assumed that the end day was 31 December. If the medication end day, month and year is missing, it will be assumed that the medication was ongoing at the end of the study, and the date will appear as missing in the data.

6.12.4 Conventions regarding time of day for efficacy assessments and concomitant medication

Efficacy assessments

For the purpose of assigning trial periods to efficacy assessments, the convention will be that efficacy assessments are performed at time 00:00:00 in the morning. Consequently, efficacy assessments performed on the day of transfer between two periods will be assigned to the first of the two periods.

Concomitant medication

For the purpose of associating concomitant medication with trial periods, the convention will be that the start time of day of concomitant medications is 23:59:59, and end time is 00:00:00, unless the start day is equal to the end day in which case both start and end time will be assumed to be 23:59:59. As a consequence, rescue medication starting on the day of transfer between two periods will be associated with the latter period only, and rescue medication ending on the day of transfer between two periods will be associated with the first period only (unless the start day is equal to the end day).
Unlike adverse events which are assigned to a single period based on their start date only, a concomitant medication can be associated with more than one period.

6.12.5 Treatment Completers

A subject who has performed Week 50 will be defined as a treatment completer.

6.12.6 Early termination and unscheduled visits

When no data is available from a certain scheduled post-baseline visit for a subject, data from early termination visits and unscheduled visits have the potential to replace data from that scheduled visit in data summaries, provided the data is collected between 6 days before and 7 days after the planned time point for the scheduled visit, as displayed below.

Visit (Target day)	**Visit window (Day is date of assessment minus date of first dose)**
Week 2 (Day 14)	Day 8 to 21
Week x (Day 7*x) (where x= 4, 6, 8, ..., 52)	Day 7*x-6 to 7*x+7
Safety follow-up	106-119 days after last dose

When both unscheduled and early termination visits exist within the given visit window, the early termination visit will be selected for analysis. When no early termination visit and

several unscheduled visits exist, the unscheduled visit closest to the target day will be selected for analysis. If the difference is a tie, the latest unscheduled visit will be selected.

6.12.7 Handling drop-outs and missing values

Missing values will be handled as described in the Clinical Trial Protocol with exception of the modified imputation methods used for the treatment policy estimand due to sparseness of data, as described in section 6.7.3.

Week 16 LOCF

As specified in the protocol, a sensitivity analysis of the primary endpoint will impute Week 16 missing values using LOCF. The LOCF value will be defined as the last assessment obtained up to and including day 7*16+7=119 after the first dose, i.e. the last assessment before or within the window for mapping an early termination visit to Week 16.

6.12.8 Treatment labels

Table 5: Treatment labels for the clinical trial report text and tables

Period	Label Used in Text	Label Used in Tables	Order in Table
Initial period	Tralokinumab 150 mg Q2W	Tralokinumab 150 mg Q2W	1
Initial period	Tralokinumab 300 mg Q2W	Tralokinumab 300 mg Q2W	2
Initial period	Placebo	Placebo	3
Maintenance period	Week 16 Tralokinumab 150 mg Q2W responders: Tralokinumab 150 mg Q2W	Week 16 Tralokinumab 150 mg Q2W responders: Tralokinumab 150 mg Q2W	1
Maintenance period	Week 16 Tralokinumab 150 mg Q2W responders: Tralokinumab 150 mg Q4W	Week 16 Tralokinumab 150 mg Q2W responders: Tralokinumab 150 mg Q4W	2
Maintenance period	Week 16 Tralokinumab 300 mg Q2W responders: Tralokinumab 300 mg Q2W	Week 16 Tralokinumab 300 mg Q2W responders: Tralokinumab 300 mg Q2W	3

Maintenance period	Week 16 Tralokinumab 300 mg Q2W responders: Tralokinumab 300 mg Q4W	Week 16 Tralokinumab 300 mg Q2W responders: Tralokinumab 300 mg Q4W	4
Maintenance period	Week 16 Placebo responders: Placebo	Week 16 Placebo responders: Placebo	5
Open-label period	Tralokinumab Q2W + optional TCS	Tralokinumab Q2W + optional TCS	1

6.12.9 Protocol deviations

Only major protocol deviations will be summarized and listed.
Protocol deviations for sites PPD and PPD will be reviewed and presented separately as data from these sites is not included in the analyses data sets.

During the blind review of data each protocol deviation and any violation of the defined inclusion/exclusion eligibility criteria will be reviewed. Protocol deviations potentially affecting confirmatory endpoints will be considered critical.

In the analysis set definition document, made prior to unblinding of the trial, documentation of any exclusions from analysis data sets will be made and each critical protocol deviation will have a reason for excluding or not excluding the subject from the FAS.

7 References

1. White IR, Daniel R, Royston P. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical variables. Computational Statistics and Data Analysis 54 (2010): 2267-2275.

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3. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983. 1983 Jun;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.

4. Vandesompele J, at al. Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. *Genome Biol* **3,** research0034.1 (2002). https://doi.org/10.1186/gb-2002-3-7-research0034.

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